

Editorial Commentary

C-Reactive Protein and Its Role in Preeclampsia

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See related article, pp 430–439

Preeclampsia is a disease characterized by increased antiangiogenesis and inflammation. Although clearly the onset of the disease is of placental origin, a network of unfavorable responses is released. Soluble variants of the vascular endothelial growth factor receptor 1 and of the tumor growth factor- β coactivating receptor endoglin are involved in the antiangiogenic response, yet the inflammatory response is complex involving multiple cytokines. Clearly, cytokines such as interleukin-6 and tumor necrosis factor- α are elevated in preeclampsia.¹ These cytokines support the expression of the acute-phase protein C-reactive protein (CRP). Regularly produced in the liver, CRP has also been found in amniotic fluid. This suggested local production sites, which were specified in the current study by Parchim et al.² As it binds to surface phosphocholine, it activates the complement system.

For a long time, a role of CRP in preeclampsia has been conceived. Studies exploring genetic variants of CRP linked to adverse cardiovascular outcomes could identify an association of these variants to preeclampsia in independent populations.³ Several studies suggested preeclampsia to be related to CRP levels and a metaanalysis exploring studies with a prospective setup to correlate CRP concentrations with the subsequent occurrence of preeclampsia, a highly significant relationship was identified with an important modifier being body mass index.^{4,5} As CRP is found elevated before disease onset,^{4,6} a pathomechanistic role could be considered. However, the functional role of CRP in preeclampsia had remained enigmatic.

In several elegant experiments, Parchim et al.² unravel a mechanism which might account for placental and also for kidney injury and arterial hypertension in preeclamptic disease. The authors demonstrate the placenta as production site for CRP in addition to the liver in nonpregnant conditions. In a classical setup, they infused CRP at concentrations comparable to those found in the circulation of preeclamptic women into mice, which led to hypertension, glomerular damage, and associated proteinuria as well as to features of premature atherosclerosis within the placentas. This was also linked to enhanced soluble vascular endothelial growth factor receptor 1 secretion.

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As the response was only seen in pregnant mice, in these short-term experiments the placenta seems to be critical.

To identify the signaling pathway, the authors referred to the observation that CRP binds to phosphocholine. As the placenta is one of the tissues to which a phosphocholine transferase activity has been localized, posttranslational phosphocholine modification might apply. As the neurokinin 3 receptor is thought to be also involved in hypertension in pregnancy and phosphocholinated neurokinin B preferentially binds to this receptor, this pathway was explored. In the mice, neurokinin 3 receptor blockade improved the tissue lesions within the kidney and within the placenta, as well as soluble vascular endothelial growth factor receptor 1 levels on CRP exposure. Knockdown of the phosphocholine transferase enzyme production resembled these findings. They found CRP and neurokinin B colocalized in villous syncytiotrophoblast cells and even identified a link between CRP, neurokinin 3 receptor signaling, and sFlt-1 secretion in human placental villus explants.

These findings are of interest for various reasons. First, they provide a link between proinflammatory markers but also maternal conditions such as an elevated body mass index with enhanced CRP levels and development of preeclampsia. This is exiting because inflammation is considered a secondary event in most forms of preeclampsia, yet high body weight might arise as an independent initial event in the pathogenesis of preeclampsia as it predisposes to higher CRP levels. Yet beyond pregnancy, if exposure to CRP is prolonged beyond acute infectious defense responses, and as more conditions and organs might be identified as phosphocholine transferase

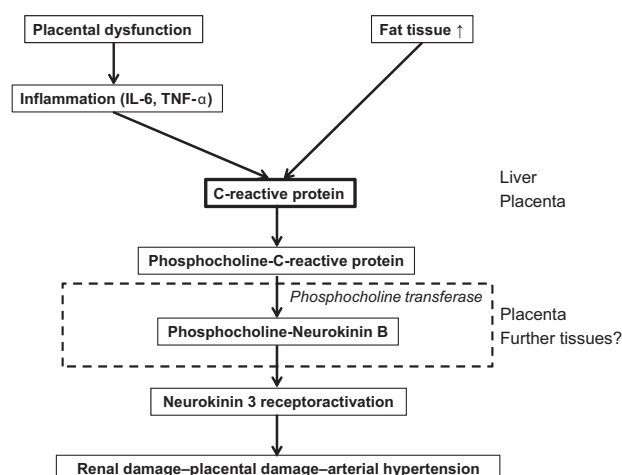


Figure. Placental dysfunction or fat tissue leads to the expression of the C-reactive protein in the liver or the placenta. C-reactive protein binds to phosphocholins which are transferred to neurokinin B thereby enhancing activation of the neurokinin 3 receptor. This leads to organ damage and arterial hypertension. IL indicates interleukin; and TNF, tumor necrosis factor.

targets such as the kidneys, the pathomechanistic role of CRP in even low level inflammation may deserve increased attention. The mechanism and the signaling pathway demonstrated in this article might even lead to future clinical applications. This is an intriguing example of how a putative predictor of disease turns into an attractive therapeutic target (Figure).

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Disclosures

None.

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